NMC Case Report Journal 2019; 6: 61–64
DOI: 10.2176/nmccrj.cr.2018-0223

Case Report

A Case of Sarcoidosis-lymphoma Syndrome: Importance of Brain Biopsy

Tomoyasu Yamanaka,[1,2] Hideki Kanai,[2] Noritaka Aihara,[1] Takayuki Ohno,[2] and Mitsuhito Mase[1]

Sarcoidosis is occasionally associated with malignant lymphoma. Cases of sarcoidosis associated with malignant lymphoma are called sarcoidosis-lymphoma syndrome. We report a 63-year-old man with sarcoidosis associated with primary central nervous system lymphoma (PCNSL). Definitive diagnosis by clinical and radiological findings was difficult. Finally, brain biopsy could produce the correct diagnosis. We could provide appropriate treatment for PCNSL and the patient has survived over 2 years. Thus, it is very important to make an early definitive diagnosis by biopsy for intracranial lesion, because it can prolong survival in patients with sarcoidosis.

Keywords: primary central nervous system lymphoma, sarcoidosis-lymphoma syndrome, sarcoidosis, biopsy, differential diagnosis

Introduction

Sarcoidosis is a disease of unknown origin that systemically forms noncaseating epithelioid granuloma and may involve any organ of the body. Common sites are the lungs, lymph nodes, skin, and eyes, and a few cases involve the nervous system. In 1972 Brincker[1)] reported that sarcoidosis was frequently associated with malignant tumors as it involved abnormality in cell-mediated immunity. Among sarcoidosis cases, one case associated with malignant lymphoma was named sarcoidosis-lymphoma syndrome in 1986.[2)] Greiner[3)] first reported a case of lymph node sarcoidosis with primary central nervous system lymphoma (PCNSL) through an autopsy in 2010. Here, we report a case of lung sarcoidosis with PCNSL who was diagnosed through brain biopsy. We emphasize that the early definitive diagnosis by biopsy for intracranial lesion is useful.

Case Report

A 63-year-old male complained of continuous fever of 38° and coughing. Chest X-ray and computed tomography (CT) revealed glass opacity in bilateral lower lung lobes. The size of the opacity had increased after 3 months and solid nodular lesions had appeared (Figs. 1A and 1B). He underwent partial lung resection. He was diagnosed as having sarcoidosis by histological findings (Figs. 1C and 1D). The findings on the chest CT improved after steroid treatment. He received intravenously 125 mg methylprednisolone for 3 days from seventh to ninth postoperative days. Steroid was tapering gradually and he received orally 10 mg prednisolone daily. Two months after the operation, the patient suffered left hemiparesis. CT revealed an intracranial lesion in the right frontal region. T_1-weighted enhanced magnetic resonance imaging (MRI) revealed an incomplete ring-shaped lesion. The meninges around the lesion were enhanced (Fig. 2). Perfusion weighted image (PWI) revealed that the lesion had low blood volume. Diffusion weighted image (DWI) revealed high signaling with a low apparent diffusion coefficient inside the lesion. The high signal lesion rapidly increased after 2 days (Fig. 3). Findings of primary tumor or lymphadenopathy were not observed in systematic contrast-enhanced CT. Hematological examination revealed no elevation in serum angiotensin converting enzyme (ACE) and a slight elevation in serum lysozyme. Neither elevation of ACE nor lysozyme were observed in the cerebrospinal fluid (CSF). CSF cultures of bacteria were negative. Indian ink preparation and mycobacterium smear were negative and tumor cells such as metastatic brain tumors and malignant lymphoma were not observed in microscopic examination.

We finally performed a biopsy on the intracranial lesion. Macroscopically, the brain around the lesion was gray. The lesion was solid. Pathological examination revealed slightly large atypical naked cells proliferating and aggregating around the blood vessels, surrounded by necrotic tissues (Figs. 4A and 4B). A diagnosis of diffuse large B cell lymphoma was obtained because CD20 and CD79α were immunohistochemically positive (Figs. 4C and 4D). The patient received high-dose methotrexate therapy with whole brain radiotherapy and has survived over 2 years.

Discussion

Based on the clinical course of this case, the differential diagnosis was neurosarcoidosis. Neurological symptoms due to central nervous system involvement develop in about 5% of patients with systematic sarcoidosis.[4)] MRI shows the occurrence of leptomeningeal involvement in 40% of patients with neurosarcoidosis.[5)] Patients with leptomeningeal involvement are known to have the following CSF findings: 40–70% exhibit pleocytosis; 40–73% have elevated protein; and 10–20% have low glucose.[6)] Parenchymal mass lesions or granulomas are a fairly common manifestation of neurosarcoidosis. Although

[1]Department of Neurosurgery, Nagoya City University, Nagoya, Aichi, Japan;
[2]Department of Neurosurgery, Nagoya City East Medical Center, Nagoya, Aichi, Japan

Received: September 7, 2018; Accepted: December 10, 2018
Online March 21, 2019

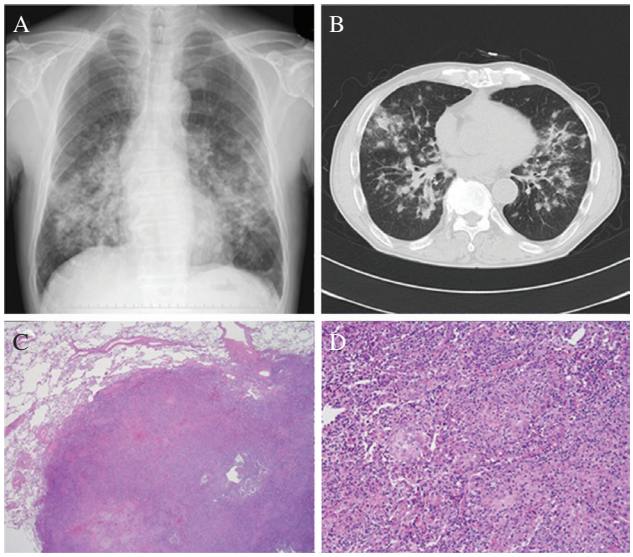

Fig. 1 Followed-up Chest X-ray (A), Chest CT scan (B) and H & E-stained photomicrographs of tissue from the resected lung (C and D). (A) Chest X-ray shows the decrease of permeability in the middle and lower lung fields. (B) Chest CT scan shows diffusely ground glass opacity on both sides of the lung. Extensively small and medium nodules are recognized, and adjacent nodules tend to fuse. (C) Lower (×20) and (D) high (×200) power field photomicrographs shows giant nodular lesions around inflammatory cells, mainly lymphocytes and plasma cells, and granuloma consisting of epithelial hyperplasia. They reveal not caseous necrosis but partially denaturation and necrosis.

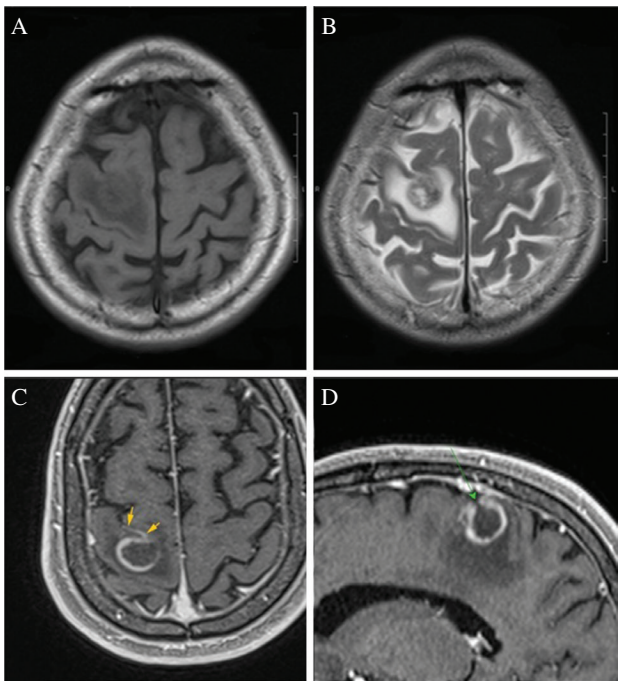

Fig. 2 MRI before brain biopsy. MRI demonstrates low signal on T_1-weighted image (A) and mixed low and slight high signal with perifocal edema on the T_2-weighted image (B) in the right precentral gyrus. Post contrast-enhanced MRI (C: axial image, D: coronal image) demonstrates ring-enhanced mass and enhancement along the meninges. Part of the ring is interrupted and it looks like "Open-ring". MRI: magnetic resonance imaging.

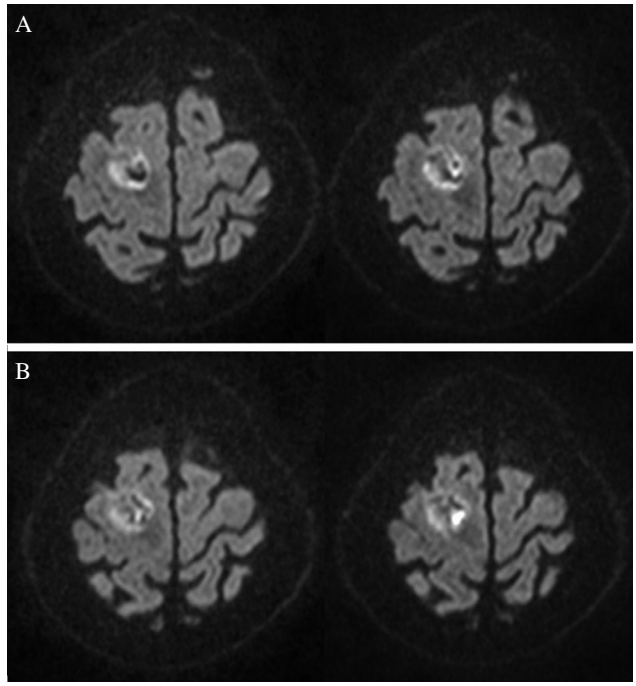

Fig. 3 Magnetic resonance imaging diffusion weighted image (DWI) (A: on admission, B: 2 days later). DWI revealed high signaling with a low apparent diffusion coefficient inside the lesion on admission, and the high signal lesion rapidly increased after 2 days.

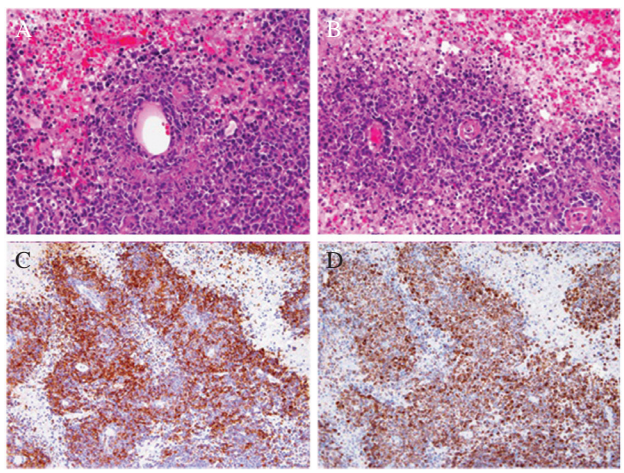

Fig. 4 H & E-stained (A and B: ×400) and immunohistochemistry (C and D: ×200) of tissue from biopsy. Photomicrograph reveals diffuse slightly large naked atypical cells increasing around the blood vessels (A) also with surrounding necrosis (B). Immunohistological staining of CD20 (C) and CD79α (D) reveal positive cells.

there is no report of neurosarcoidosis appearing when pulmonary lesions improved with steroid treatment, the possibility cannot be completely ruled out.

High-grade glioma, and brain abscess were also considered as a differential diagnosis for this case. Rapid increase of high signaling area on DWI after steroid therapy suggest brain abscess in general. Proton MR spectroscopy (^{1}H-MRS) in patients with brain abscess shows high peaks of lactic acid and cytosolic amino acid, indicating anaerobic metabolism.[7)]

Table 1 Comparison with the past case that was reported as primary central nervous system lymphoma (PCNSL) with sarcoidosis

Author (Year)	Age (years)/ Sex	Location of sarcoidosis	Symptom of PCNSL	MRI findings	How to diagnose	Steroid treatment	Survival time after initial symptom
Greiner et al. (2010)[3]	69/-	Mediastinal lymph nodes	Decreasing level of conscious	Periventricular enhanced mass lesion	Autopsy	Intravenously high-dose dexamethasone	38 days
Present case	63/M	Lung	Left hemiparesis	Enhanced incomplete ring-shaped lesion	Biopsy	Intravenously 125 mg methyl-prednisolone for 3 days and, gradually tapering, orally 10 mg prednisolone daily	>2 years

MRI: magnetic resonance imaging.

We performed ^{1}H-MRS and findings of anaerobic metabolism were not observed in this case. Low blood flow at the lesion on PWI also suggested the unlikelihood of high-grade glioma or metastatic brain tumor.[8,9] However, we could not reach a definitive diagnosis without a specimen.

It is assumed that sarcoidosis causes abnormal cellular immunity and the immune system's defense against malignant tumors to fail.[10,11] These mechanisms may be a reason that malignant lymphoma and other malignant tumors follow the onset of sarcoidosis.[12] The association of sarcoidosis and malignant lymphoma is well known as sarcoidosis-lymphoma syndrome.[2] Nevertheless, we did not anticipate malignant lymphoma before surgery in this case. Malignant lymphoma exhibits a variety of imaging findings.[13,14] Contrast-enhanced MRI shows malignant lymphoma to be homogenously contrasted in general,[15] unlike this case. Approximately 10% of patients show no contrast of the lesion. "Open-ring" enhancement as in this case sometimes (0–13%) appears with acquired immune deficiency syndrome or in immunosuppressed patients.[16] It is known that intracranial malignant lymphoma develops multiple lesions in the majority of immunosuppressed patients and even in 20–40% of immunologically normal patients.[16,17] On MRI, equivalent or low signal intensity is typically observed on T_1-weighted images, and high signal intensity is observed on T_2 or FLAIR weighted images.[15] Although steroid treatment may affect MRI findings, these findings are not specific to malignant lymphoma. Therefore, brain biopsy was needed for the definitive diagnosis in our case.

To the best of our knowledge, Greiner[3] reported the first case of lymph node sarcoidosis with PCNSL through autopsy in 2010. The patient had progressive cranial nerve dysfunctions and decreasing level of consciousness while no acute cerebral lesions had been noted on MRI. He was clinically diagnosed as neurosarcoidosis because of spreading mediastinal lymph nodes and had undergone treatment with steroids and immunosuppressive agents. Under the influence of such treatments, he died of multiple organ failure due to sepsis 38 days after introduction. At autopsy, a diagnosis of PCNSL was made because lymphohistiocytic and lymphoblastic elements with CD20 positive diffusely infiltrated the brain parenchyma and no lymphoma manifestation was detected in other organs. Furthermore, the enlarged mediastinal lymph nodes turned out to be lymph node sarcoidosis.

We consider early definite diagnosis to be important because the treatment for malignant lymphoma differs completely from that for neurosarcoidosis. We also believe that early definite diagnosis contributes to survival because appropriate treatment can be provided. The association of sarcoidosis with malignant lymphoma should be recognized. Interleukin-10 (IL-10) in CSF is reported to be higher than that of other brain tumors.[18] Tumor markers, such as IL-10 in CSF and serum-soluble interleukin-2 receptor[19] and serum beta 2-microglobulin,[20] should have been examined and these findings might be helpful for diagnosis. However, making a definite diagnosis needs specimens and we stress the importance of biopsy.

Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional conflicts of interest in this case report. The authors, who are members of the Japan Neurosurgical Society (JNS), have registered online and filled out the Self-reported COI Disclosure Statement Forms through the JNS members' website.

References

1) Brincker H: Sarcoid reactions and sarcoidosis in Hodgkin's disease and other malignant lymphomata. *Br J Cancer* 26: 120–123, 1972
2) Brincker H: The sarcoidosis-lymphoma syndrome. *Br J Cancer* 54: 467–473, 1986
3) Greiner EJ, Mügge LO, Romeike BF, et al.: A case with coincidental diagnosis of primary central nervous system lymphoma and lymph node sarcoidosis. *J Neurooncol* 99: 129–134, 2010
4) Nowak DA, Widenka DC: Neurosarcoidosis: a review of its intracranial manifestation. *J Neurol* 248: 363–372, 2001
5) Ginat DT, Dhillon G, Almast J: Magnetic resonance imaging of neurosarcoidosis. *J Clin Imaging Sci* 1: 15, 2011
6) Lacomis D: Neurosarcoidosis. *Curr Neuropharmacol* 9: 429–436, 2011
7) Lai PH, Hsu SS, Ding SW, et al.: Proton magnetic resonance spectroscopy and diffusion-weighted imaging in intracranial cystic mass lesions. *Surg Neurol* 68 Suppl 1: S25–S36, 2007
8) Toh CH, Wei KC, Chang CN, Ng SH, Wong HF: Differentiation of primary central nervous system lymphomas and glioblastomas: comparisons of diagnostic performance of dynamic susceptibility contrast-enhanced perfusion MR imaging without and with contrast-leakage correction. *AJNR Am J Neuroradiol* 34: 1145–1149, 2013
9) Xu W, Wang Q, Shao A, Xu B, Zhang J: The performance of MR perfusion-weighted imaging for the differentiation of high-grade glioma from primary central nervous system lymphoma: A systematic review and meta-analysis. *PLoS One* 12: e0173430, 2017
10) Cohen PR, Kurzrock R: Sarcoidosis and malignancy. *Clin Dermatol* 25: 326–333, 2007
11) London J, Grados A, Fermé C, et al.: Sarcoidosis occurring after lymphoma: report of 14 patients and review of the literature. *Medicine* (*Baltimore*) 93: e121, 2014

12) Linnenberg HS, Medici TC, Rhyner K: [The "sarcoidosis-lymphoma syndrome"—a lymphocyte dysregulation?]. *Pneumologie* 46: 229–235, 1992 (German)
13) Coulon A, Lafitte F, Hoang-Xuan K, et al.: Radiographic findings in 37 cases of primary CNS lymphoma in immunocompetent patients. *Eur Radiol* 12: 329–340, 2002
14) Erdag N, Bhorade RM, Alberico RA, Yousuf N, Patel MR: Primary lymphoma of the central nervous system: typical and atypical CT and MR imaging appearances. *AJR Am J Roentgenol* 176: 1319–1326, 2001
15) Adachi K, Yamaguchi F, Node Y, Kobayashi S, Takagi R, Teramoto A: Neuroimaging of primary central nervous system lymphoma in immunocompetent patients: comparison of recent and previous findings. *J Nippon Med Sch* 80: 174–183, 2013
16) Zhang D, Hu LB, Henning TD, et al.: MRI findings of primary CNS lymphoma in 26 immunocompetent patients. *Korean J Radiol* 11: 269–277, 2010
17) Haldorsen IS, Espeland A, Larsson EM: Central nervous system lymphoma: characteristic findings on traditional and advanced imaging. *AJNR Am J Neuroradiol* 32: 984–992, 2011
18) Sasayama T, Nakamizo S, Nishihara M, et al.: Cerebrospinal fluid interleukin-10 is a potentially useful biomarker in immunocompetent primary central nervous system lymphoma (PCNSL). *Neuro-oncology* 14: 368–380, 2012
19) Murakami S: Soluble interleukin-2 receptor in cancer. *Front Biosci* 9: 3085–3090, 2004
20) Aulbert E, Steffens O: [Beta 2 microglobulin in serum—a "tumor marker" in malignant lymphomas?] *Med Klin* (*Munich*) 85: 13–17, 1990 (German)

Corresponding author:
Tomoyasu Yamanaka, MD, Department of Neurosurgery, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, Aichi 467-8601, Japan.
✉ tomo1202@med.nagoya-cu.ac.jp